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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,285	07/03/2003	Richard Derek Iggo	604-689	5824

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/612,285	IGGO ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/433,681.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20030703*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment filed 7/3/03 and the amendments filed 2/20/04 have been entered.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

Priority is claimed to application 10/433,681 filed 12/23/03, whereas the instant application has an earlier filing date of 7/3/03. Consequently, the instant application cannot claim priority to the '681 application.

The declaration filed 2/20/04 indicates that priority is being claimed to PCT/GB02/03211 filed 7/12/02 under 35 U.S.C. 120, but does not indicate the relationship to the instant application. A putative priority claim lacking the relationship is not treated as an actual priority claim. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included. In this case, it appears the instant application is a continuation-in-part of the PCT application.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Claim Objections

Claims 5, 21 and 29 are objected to because of the following informalities. Claim 5 uses improper Markush format; --from the group consisting of-- should be inserted after "selected from;" also the thymidine kinase, etc. are proteins not genes, insertion of --encodes a protein-- after "gene" is suggested. In claim 21, "Tcf-4, RBPJK, Gli-l, HIFlalpha and telomerase promoter binding sites" should be "a Tcf-4, a RBPJK, a Gli-l, and a HIFlalpha promoter binding site and a telomerase promoter-- ; the first three are transcription factors, telomerase is not (see para. bridging pp. 2-3 of spec.). In claim 29, line 3, "comprisng" is a misspelling

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 16, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for insertion of the therapeutic or suicide gene into the adenoviral major late transcription unit after the L5 (fibre) gene (claims 6, 16, and 22) or into adenoviral E3 under control of the E3 promoter (claim 22), does not reasonably provide enablement for any other site of insertion of the therapeutic or suicide gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 6 broadly requires that the therapeutic gene is expressed late in replication of the adenovirus using an IRES or by differential splicing. Claim 16 broadly requires expression in a replication-dependent manner from the major late transcription unit. Claim 22 broadly requires that the expression be in a replication dependent manner. The specification provides guidance and working examples for only two ways of constructing an adenovirus with these properties. The first way, which applies to all three claims, is to insert the gene into the major late transcription unit between the L5 gene and the E4 region, i.e. at the 3' end of the major late transcription unit. In addition, the therapeutic gene is operably linked to the L5 coding sequence with an IRES or operably linked to a splice acceptor site to create a new splicing unit in the major late transcription unit. The specification (page 16, lines 1-2) discloses Applicant's belief that such a modification is novel and inventive. There is no prior art of record that those of skill in the art were aware of how one could make a conditionally replicative adenovirus that expressed a transgene late in replication or from the major late transcription unit. While the insertion site described in the specification is not opposite any essential genes, the L1-L5 genes are opposite and overlap essential genes, such as the E2 region.

The second way, which applies only to claim 22, is to insert the gene into E3 under control of the E3 promoter, which is regulated by an E1A gene product, and so in a replication dependent manner.

The specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Therefore, in view of the lack of prior art teachings on how to make a conditionally replicative adenovirus with the required characteristics and

guidance and working examples limited to the embodiments indicated above it would clearly require undue experimentation to devise alternative adenovirus wherein the therapeutic gene was inserted elsewhere than in the major late transcription unit following the L5 gene.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

There is insufficient antecedent basis for the following limitations in the claims.

1) Claim 1 recites the limitations "the E1A open reading frame" and "said selected transcription factor" in lines 3-5.

2) Claim 2 recites the limitations "the fibre gene," "the E4 region" and "the major late transcription unit" in lines 2-3.

3) Claim 4 recites the limitation "the wild type packaging signal" and "the left hand inverted repeat" in lines 1-3.

4) Claim 8 recites the limitations "the E4 promoter," "the E1A enhancer," and "the packaging signal" in lines 1-2.

5) Claim 12 recites the limitations "the viral promoter sequences" and "the tumor specific transcription factor" in lines 4-5.

6) Claim 13 recites the limitations "the selected transcription factor," "the E1A open reading frame," and "said selected transcription factor" in lines 1-3.

7) Claim 14 recites the limitations "the wild type packaging signal" and "the left hand inverted terminal repeat" in lines 1-3.

8) Claim 16 recites the limitation "the major late transcription unit" in lines 2-3.

9) Claim 20 recites the limitation "the E1B, E2, and E3 open reading frames" and "said selected transcription factor" in lines 3-5.

10) Claim 24 recites the limitations "the right hand terminal repeat" and "the left hand ITR" in lines 2-3.

11) Claim 29 recites the limitations "the replacement with tumor specific transcription factor" in lines 5-6. Insertion of --binding sites-- after "factor" is suggested.

Most of these result from the base claim not reciting what adenoviral sequences, at minimum, are present, or whether what sequences are present are wild-type.

Claim 24 does not make sense. The specification only discloses this limitation in the context of an adenovirus having the E1A enhancer and packaging sequence being replaced with selected transcription factor binding sites, and inserting the same binding sites at the right ITR for symmetry. Claim 20, from which claim 24 depends, does not require that the there be such sites at the left ITR. If the wild type packaging sequence and E1A promoter are intact, placing binding sites in the right ITR would disrupt symmetry, not preserve it. It is unclear if claim 24 requires modification of the E1A promoter as well.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (f) he did not himself invent the subject matter sought to be patented.

Claims 1, 3, 4, 7, 9-15, 17-22, and 24-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Iggo et al., WO 00/56909.

Iggo et al. discloses a DNA construct encoding an adenoviral genome that generically has one or more early viral genes, e.g. E2 genes, under control of a promoter comprising one or more heterologous transcription factor binding sites that binds a transcription factor that is expressed at higher levels in a tumor cell than in a normal cell of the same type, such as a Tcf-4, RBPJk, Gli-1 or HIFα transcription factor binding site or a part of a telomerase promoter that confers tumor–specific transcription. The heterologous transcription factor binding site may replace wild-type viral promoter sequences, and multiple copies of the binding site may be inserted, e.g. 2-20 copies of a Tcf-4 binding site. The adenoviral genome may be derived form Ad5, Ad40 or Ad41, or incorporate DNA encoding an Ad40 or Ad41 fiber protein. The adenoviral genome preferably retains a functional viral RNA nuclear export capability by retention of the E1B 55k protein gene and E4 ORF6.

Iggo focuses more specifically on modification of at least the E2 promoter. Where the E2 early promoter is modified, the E3 promoter may be mutated to inactivate one or more of its NF1, NFκB, AP1 or ATF sites, and the E2 late promoter may be inactivated by mutations that are silent in the overlapping 100k protein coding sequence. In some embodiments (page 13), the

E1A promoter is replaced with a promoter comprising the heterologous binding sites to further restrict replication of the adenovirus to tumor cells. In these embodiments, the packaging sequence, which has overlapping E1A promoter sequences, is moved to the right ITR, which is adjacent to the E4 promoter and the right repeat is also modified with the transcription factor binding sites. A therapeutic gene, such as a gene encoding a prodrug activating enzyme such as HSV tk or cytosine deaminase, can be included in the adenoviral genome under control of the E3 promoter, which is regulated in a replication-dependent manner normally by E1A, and when E1A is under control of a heterologous transcription factor binding site.

Iggo teaches making the constructs by cloning the adenoviral genome into a YAC/BAC in yeast by gap repair, then modifying the adenoviral genome by a two-step gene replacement process, then transferring the construct to bacteria for amplification of the construct, followed by transfection of a suitable mammalian cell line for production of adenovirus. Iggo teaches using the adenovirus for treating patients having neoplasms, such as colon cancer and liver metastases of colon cancers wherein the heterologous transcription factor binding site is a Tcf-4 binding site.

See entire document, especially pages 6-17, 22-31, and claims 1-36.

Similar rejections also could be made under 35 USC 102(e) over US 6,544,507, which is a 371 application of the PCT corresponding to WO 00/56909, and provisionally under 35 USC 102(e) over U.S. application 10/376,630, which is a CON of the '507 patent. However, such rejections would be superfluous in light of the rejection over WO 00/56909 set forth above.

Claims 1, 3, 4, 7, 9-15, 17-22, and 24-30 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. US 6,544,507 and US application 10/376,630, which is a CON of the '507 patent with the same disclosure, share inventor Iggo with the instant application, but not the same inventive entity, and are currently commonly assigned with the instant application. Claims 1-23 of U.S. Patent No. 6,544,507 are directed to an adenoviral DNA construct etc. wherein at least the E2 region is under control of a selected transcription factor binding site, e.g. a TCF-4 binding site. The claims are not explicitly directed to a construct wherein the E1A region is also under control of a selected transcription factor binding site or where the adenovirus also expresses a suicide gene. However, when the patent claims are read in light of the supporting disclosure in the patent specification, specifically at col. 8, line 45, to col. 9, line 4, the claims clearly embrace embodiments wherein the E1A genes, in addition to the E2 genes, are under control of a selected transcription factor binding site and a suicide gene, such as encoding HSV tk or cytosine deaminase. This part of the patent also describes the modifications of moving the packaging signal to the right terminal region of the recombinant adenoviral genome and adding the binding sites t the right end as well. Claim 37 of the '630 application explicitly claims such embodiments wherein the selected binding sites are Tcf-4 binding sites. Claims 1, 3-10, 14-21, 23, 26-29, and 32-36 of the '630 application are directed to the embodiments with the same limitations as in the instant claims. These embodiments implicitly and explicitly claimed in the '507 patent and '630 application are embraced by the instant claims.

The issue of priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f) of this single invention must be resolved.

Since the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302), the assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f) or (g) and not an extension of monopoly.

Failure to comply with this requirement will result in a holding of abandonment of this application.

Double Patenting

Applicant is advised that should claim 3 be found allowable, claim 13 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 1, 3, 4, 7, 9-15, 17-22, and 24-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,544,507. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims embrace an explicitly disclosed embodiment of the patented claims. The claims of the '507 patent do not explicitly claim viral DNA constructs, etc. that comprise a selected transcription factor binding site operably linked to the adenoviral E1A

genes in addition to the an E2 region under control of a selected transcription factor binding site. However, when the patent claims are read in light of the supporting disclosure in the patent specification, specifically at col. 8, line 45, to col. 9, line 4, the claims clearly embrace an embodiment wherein the E1A genes, in addition to the E2 genes, are under control of a selected transcription factor binding site. This part of the patent also describes the modifications of moving the packaging signal to the right terminal region of the recombinant adenoviral genome, and simultaneous modification of both terminal repeats with the transcription factor binding sites.

Claims 1, 3, 4, 7, 9-15, 17-22, and 24-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-10, 14-21, 23, 26-29, and 32-37 of copending Application No. 10/376,630. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claim 37 of the '630 application explicitly claims an embodiment of instant claim 1, for example, wherein the selected binding sites are Tcf-4 binding sites. Claims 3-10, 14-21, 23, 26-29, and 32-36 of the '630 application are directed to the embodiments with the same secondary limitations as in the instant claims, but do not require that the E1A genes also be under control of the selected binding site, as in claim 37. However, the instant claims embrace the embodiments of claim 37 of the '630 application that also have the limitations set forth in claims 3-10, 14-21, 23, 26-29, and 32-36 of the '630 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 10/433,681. Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant invention differs from that of the '681 application in requiring a therapeutic gene. However, when the claims of the '681 application are read in light of the supporting disclosure in its specification (page 15), they clearly embrace embodiments wherein a suicide gene is present and where it is inserted between the fibre gene and E4 region using an IRES or alternative splicing.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe, Ph.D.
Primary Examiner
Art Unit 1633